

### ***Remarks***

#### ***I. Status of the Claims and Support for the Amendments***

Claims 1, 10, 17-20, 23, 24, 26, 28, 29 and 52-54 have been amended herein. Support for the amendment is found in the present Specification and original claims.

Claims 2-9, 11-17 and 30-51 have been canceled herein without prejudice to or disclaimer of the subject matter therein.

No new matter has been added by this amendment.

#### ***II. The Novelty Rejection Over Claeson In View Of Elgendy Should Be Withdrawn***

At page 3 of the Office Action, the Examiner rejected claims 1-7, 10-12, 14 and 15 for lack of novelty under 35 U.S.C. § 102(b) over Claeson *et al.*, U.S. Patent No. 5,856,306 (hereinafter "Claeson") "as evidenced by" Elgendy *et al.*, *The Design of Synthetic Inhibitors of Thrombin*, pages 173-178, Plenum Press, New York (1993) (hereinafter "Elgendy"). Applicants respectfully traverse this rejection.

Claims 2-7, 11, 12 and 14 have been canceled. With respect to claims 1 and 10, Applicants provided the following remarks.

Claim 9 was not rejected. Claim 1 has been amended to incorporate the limitation of claim 9 ("base addition salt"), and claim 10 has been amended in a similar fashion. Claeson fails to teach the invention of claims 1 and 10, at least because Claeson fails to teach a base addition salt of the formula Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)<sub>2</sub>. The Examiner's reliance on Elgendy to supplement the disclosure of Claeson does not support the rejection over Claeson of the presently claimed invention.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

***III. The Obviousness Rejection Under Claeson In View Of Elgendy And Baschang Should Be Withdrawn***

At page 4 of the Office Action, the Examiner rejected claims 1-7, 10-12, 14, 15, 20, 23, 26, 28 and 52-54 under 35 U.S.C. § 103(a) as allegedly obvious over Claeson in view of Elgendy and Baschang *et al.*, U.S. Patent No. 4,959,394 (hereinafter "Baschang"). Applicants respectfully traverse this rejection. A *prima facie* case of obviousness has not been established.

Claims 2-7, 11, 12, 14 and 15 have been canceled. With respect to claims 1, 10, 20, 23, 26, 28 and 52-54, Applicants provide the following remarks.

As previously noted, claims 1 and 10 have been amended to recite a base additional salt. Like claims 1 and 10, claims 52 and 54 recite a base addition salt

None of Claeson, Elgendy or Baschang discloses a base addition salt of a boronic acid of the formula Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)<sub>2</sub>. Even in combination, Claeson, Elgendy and Baschang would not have provided the oral dosage form of claim 1, the oral pharmaceutical dosage form of claim 10, the aqueous solution of claim 52 and the aqueous solution of claim 54, each of which recites a base addition salt of Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)<sub>2</sub>.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

***IV. The Obviousness Rejection Under Claeson In View Of Elgendy, Baschang And Adams Should Be Withdrawn***

At page 6 of the Office Action, the Examiner rejected claims 8, 9, 13, 16-19 and 29 under 35 U.S.C. § 103(a) as allegedly obvious over Claeson in view of Elgendy, Baschang, and Adams *et al.*, U.S. Patent No. 5,780,454 (hereinafter "Adams").

Applicants respectfully traverse this rejection. A *prima facie* case of obviousness has not been established.

Claims 8, 9, 13 and 16 have been canceled. With respect to claims 17-19 and 29, Applicants provide the following remarks.

At page 6 of the Office Action, referring to Claeson, Elgendy and Baschang, the Examiner stated that "[n]either reference [sic] expressly teach [sic] multivalent salts of the boronic acid thrombin inhibitors."

The Examiner continued:

Adams et al. teach boronic acid thrombin inhibitors for medicinal use, and pharmaceutically acceptable formulations comprising a multivalent metal ion. Water-soluble salts are preferable, including divalent ion salts such as alkaline earth metal salts such as magnesium, calcium, etc. (e.g., col. 9 and claims).

Further, neither reference [sic] appears to specifically name the compound Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-BOH<sub>2</sub> [sic] with the stereoisomers in the Pro and Mpg as instantly claimed. With regards to the chiral centers, one of ordinary skill in the art would have been motivated to determine the chirality and also find any activity differences among stereoisomers of a given pharmaceutically active compound. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since such determinations are routinely made in the laboratory by the artisan of ordinary skill in the art and because it was known that most compounds are normally synthesized as racemic mixtures containing several stereoisomers at once.

Office Action at pages 6-7.

Applicants respectfully disagree with this analysis. In order for an obviousness rejection to be proper, it is necessary for the Examiner to identify reasons why one of ordinary skill in the art would have modified the cited art in an effort to obtain the

claimed invention. *See KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1741 (2007) ("[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."). Here, inadequate reasons have been provided why one of ordinary skill in the art would have allegedly combined the cited art in an effort to obtain the claimed invention.

Claeson relates to pinacol esters of certain boronic acids. Claeson fails to disclose the oral dosage form of independent claim 1, the oral pharmaceutical dosage form of independent claim 10, the aqueous solution of claim 52, and the aqueous solution of claim 54 (each of which recites Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)<sub>2</sub>).

Elgendy, Baschang and Adams fail to cure the deficiency of Claeson. Elgendy relates to a structure-function study of certain boronic acid inhibitors of thrombin. Baschang relates to an L-arginine salt of an acetyl aspartic acid derivative. Adams depicts a generic boronic acid structure (1a) at column 4. Adams also provides a general disclosure of pharmaceutically acceptable acid and base addition salts at column 9, lines 47-65.

None of Elgendy, Baschang and Adams discloses a base addition salt of a boronic acid of the formula Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)<sub>2</sub>.

Even in combination, Claeson, Elgendy, Baschang and Adams would not have provided the oral dosage form of claims 17-19 and the pharmaceutical formulation of claim 29 (each of which recites Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)<sub>2</sub>). Claeson encompasses hundreds, if not thousands or millions, of compounds, and there is no

guidance in Claeson, Elgendy, Baschang or Adams to pick Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)<sub>2</sub>, in particular, and make a base addition salt.

A flexible approach for establishing obviousness was set out in *KSR*. However, the present rejection is based on the sort of hindsight analysis that is prohibited under *KSR*. *See KSR* at 1742; *see also In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

Here, even if individual elements of the claimed invention arguably may be found in the art from separately cited documents, one of ordinary skill in the art, absent hindsight analysis, would have had no reason to modify Claeson's broad teaching, regarding boronic acid compounds, in an effort to obtain the claimed invention. Therefore, a *prima facie* case of obviousness has not been established.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

#### ***V. The Obviousness-Type Double Patenting Rejections***

##### ***A. The Rejection Over U.S. Patent No. 7,112,572 In View Of Baschang***

At page 8 of the Office Action, the Examiner rejected claims 1-20, 23, 24, 26, 28, 29 and 52-54 for obviousness-type double patenting over claims 1-92 of U.S. Patent No. 7,112,572 (hereinafter "the '572 patent") in view of Baschang. Applicants respectfully traverse this rejection.

Claims 2-9 and 11-17 have been canceled. With respect to claims 10, 23, 24, 26, 28, 29 and 52-54, Applicants request that this rejection be held in abeyance until otherwise patentable subject matter has been identified in the present application.



***B. The Rejection Over U.S. Patent No. 7,371,729 In View Of Baschang***

At page 9 of the Office Action, the Examiner rejected claims 1-20, 23, 24, 26, 28, 29 and 52-54 for obviousness-type double patenting over claims 1-48 of U.S. Patent No. 7,371,729 (hereinafter "the '729 patent") in view of Baschang. Applicants respectfully traverse this rejection.

Claims 2-9 and 11-17 have been canceled. With respect to claims 10, 23, 24, 26, 28, 29 and 52-54, Applicants request that this rejection be held in abeyance until otherwise patentable subject matter has been identified in the present application.

***C. The Rejection Over U.S. Application No. 10/592,265 In View Of Baschang***

At page 11 of the Office Action, the Examiner rejected claims 1-20, 23, 24, 26, 28, 29 and 52-54 for obviousness-type double patenting over claims 1-42 of U.S. Application No. 10/592,265 (hereinafter "the '265 application") in view of Baschang. Applicants respectfully traverse this rejection.

Claims 2-9 and 11-17 have been canceled. With respect to claims 10, 23, 24, 26, 28, 29 and 52-54, Applicants provide the following remarks.

M.P.E.P. § 1490.V.D. provides:

If two (or more) pending applications are filed, in *each* of which a rejection of one claimed invention over the other on the ground of provisional nonstatutory double patenting (ODP) is proper, the provisional ODP rejection will be made in each application. If the provisional ODP rejection is the only rejection remaining in the earlier-filed of the two pending applications, (but the later-filed application is rejectable on other grounds), the examiner should then withdraw the provisional ODP rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Although the international applications from which the present application and the '265 application entered the U.S. national stage were filed on the same day, the '265 application has not yet been examined. It is not yet known when or if the '265 application will issue. Therefore, it would be unfair to require Applicants to file a terminal disclaimer in the present application over the '265 application at the present time. It is submitted that withdrawing this rejection would be consistent with the spirit of M.P.E.P. § 1490.V.D.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

***V. The Information Disclosure Statement***

The information disclosure statement filed January 16, 2008 does not appear to have been considered. Applicants request that the Examiner initial and return a copy of the IDS Forms filed January 16, 2008, and indicate in the official file wrapper of this patent application that the January 16, 2008 information disclosure statement and the documents cited therein have been considered.

***Conclusion***

All of the stated grounds of rejection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the presently outstanding rejections.


Applicants believe that a full and complete reply has been made to the outstanding Office Action.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Grant E. Reed  
Attorney for Applicants  
Registration No. 41,264

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1100 New York Avenue, N.W.  
Washington, D.C. 20005-3934  
(202) 371-2600

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